Skin problems associated with pegylated liposomal doxorubicin-more than palmoplantar erythrodysesthesia syndrome

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Abstract: Liposomal pegylated doxorubicin is an encapsulation form of doxorubicin, with an improved pharmacokinetic profile and the ability to selectively accumulate into tumor tissue. As a result, the tolerated dose of the drug can be increased, followed by a reduced incidence of neutropenia and cardiotoxicity in comparison to doxorubucin treatment. However, a common adverse dose-schedule limiting effect of the treatment is palmoplantar erythrodysesthesia syndrome. In this retrospective study we included six patients hospitalised in the University Hospital of Zurich during the last 2 years, in connection with side effects caused by pegylated liposomal doxorubicin. These patients received this chemotherapeutic agent for treatment of various malignancies such as breast cancer, ovarian cancer, mycosis fungoides and cutaneous B-cell lymphoma. Three of six patients in this study developed classical palmoplantar erythrodysesthesia, one developed palmoplantar erythrodysesthesia associated with extensive bullous disease, one developed eruption of lymphocyte recovery syndrome and one developed intertrigo like dermatitis with stomatitis. Pegylated liposomal doxorubicin induces various skin reactions including palmoplantar erythrodysesthesia syndrome. However, the exact clinical presentation might depend on pre-existing skin diseases.

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Abstract

Background. Liposomal pegylated doxorubicin is an encapsulated form of doxorubicin, with an improved pharmacokinetic profile and the ability to selectively accumulate into tumor tissue. As a result, tolerated dose of the drug can be increased followed by the reduced incidence of neutropenia and cardiotoxicity in comparison to doxorubucin treatment. However, common adverse dose-schedule limiting effect of the treatment is palmoplantar erythrodysesthesia syndrome.

Design. In this retrospective study we included six patients hospitalised in the University Hospital of Zurich during the last 2 years, in connection with side effects caused by pegylated liposomal doxorubicin. These patients received this chemotherapeutic agent for treatment of various malignancies such as breast cancer, ovarian cancer, mycosis fungoides and cutaneous B-cell lymphoma.

Results. Three of six patients in this study developed classical palmoplantar erythrodysesthesia, one developed palmoplantar erythrodysesthesia associated with extensive bullous disease, one developed eruption of lymphocyte recovery syndrome and one developed intertrigo like dermatitis with stomatitis.

Conclusion. Pegylated liposomal doxorubicin induces various skin reactions including palmoplantar erythrodysesthesia syndrome. However the exact clinical presentation might depend on pre-existing skin diseases.

Key words: eruption of lymphocyte recovery, hand foot syndrome, palmoplantar erythrodysesthesia, pegylated liposomal doxorubicin, skin toxicities, stomatitis,

Introduction

Delivery systems have been developed to exploit tumor microphysiology and have aimed at improving the tropism of chemotherapeutic agent toward tumor cells [1].Therefore macromolecular carriers have been used during the past years providing the single drugs with specific characteristics, such as long circulating time capacity, preferential extravasation and accumulation in tumor stroma. Liposomal anthracyclines, such as pegylated liposomal doxorubicin (PLD) have accomplished considerable and prolonged circulation within the body based upon unique drug encapsulation, which in turn results in significant anticancer activity with reduced adverse effects, such as cardiotoxicity and neutropenia [2].

PLD is an encapsulated into polyetyelene-glycol coated liposomes variant of doxorubicin with a reduced uptake by the reticulo-endothelial system. The volume of distribution of this drug is close to blood volume and the area under the concentration-time curve (AUC) is increased at least 60 fold compared with free doxorubicin [3]. PLD has an eliminated half-life around 40-60 hours in human body and circulation time of 2-3 weeks in the blood and the drug remains encapsulated in the liposomes during this time [4].

PLD acts in a completely different manner when compared to doxorubicin in a non liposomal form. After extravasation into tumor tissue, liposomes remain within tumor cells. but they do not interact with plasma proteins and mononuclear phagocytes. Consequently, liposomes undergo enzymatic degradation, which leads to the release of the drug into the tumor tissue. During encapsulation within the liposomes, the drug is not bioavailable, hence has no anti-tumor effect and thus no therapeutic ability. On the opposite side, the therapeutic results of the medication itself and differences in these may not vary much compared to doxorubicin when the liposomes have not yet reached to the target tissues [5].Therefore

there is a correlation between efficacy and toxicity of liposomal doxorubicin and the different liposomal leakage rates.Liposomes with the best therapeutic activity are those with the slowest drug release rate [6].

The pegylated liposomal form of doxorubicin has been investigated and is used today for the treatment of metastatic breast cancer, aggressive Non-Hodgkin lymphoma, non small cell lung cancer, multiple myeloma, gastrointestinal malignancies [7]. Moreover, it is more and more often accepted as a treatment option for the acquired immunodeficiency syndrome-related Kaposi sarcoma [8] and the refractory ovarian cancer [9]. There are many side effects reported, which are connected to PLD treatment, nevertheless, skin toxicities are the most important dose limiting side effects.

We report on 6 consecutive patients with different mallignancies which were referred to or treated by the Department of Dermatology of Zurich University hospital with PLD and in turn developed cutaneous side effects, including palmoplantar erythrodysesthesia syndrome (PPE), also called hand foot syndrome (HFS) or acral erythema (AE). PPE is characterised as a patchy erythema of hands and soles, whose primary lesions can sometimes become painful, can lead to erosions and to desquamation, ulceration, blister formation and can also cause functional limitation during daily activity.

Materials and methods

Medical records of six patients treated with PLD at the University hospital of Zurich from 2005 until 2007, were retrospectively reviewed. Laboratory data including histological findings and clinical information of the skin manifestation such as clinical symptoms, location and severity of clinical signs, as well as treatment regimen were collected. Toxicity

was graded using the basic scale from the common toxic effects criteria of the National Cancer Institute for evaluation of the skin lesions (Table 1) [10].

All six patients were Caucasian women with the age range from 23 to 73 years. They received PLD in different doses-schedules as a treatment for different malignancies: three of them for metastasized breast cancer, one for ovarian cancer, one for tumor stage mycosis fungoides [11] and one for cutaneous B-cell lymphoma (Table 2). All six patients had diagnosed disease evaluated with standard criteria. Dermatologic examination was conducted at all cases and any evidence of skin toxicity was classified and documented.

Before receiving PLD five of six patients were treated with at least one chemotherapeutic agent. Only one patient had received anthracyclines in the past, with no reported side effect. Also no allergic side effects occurred during infusion of PLD. PLD was administered as a 1-2 hours intravenous infusion. The cycles were repeated every four weeks, except in two cases, in which they repeated every two weeks. One patient received oral corticosteroids, as prophylactic treatment of PPE before the infusion.

Results

Clinical presentations and severity

Three of six patients in this study developed classical PPE, one PPE associated with bullous disease on pre-existing scars due to prurigo nodularis, one developed eruptions of lymphocyte recovery (ELR) and one showed intertrigo-like dermatitis with stomatitis. In five of six patients the manifestations were located on the palms and soles, in three patients they were located also at the intertriginous areas of the body and one showed infiltration of the oral mucosa (Table 2). Two of the patients developed Grade III skin lesions, one of which was compatible with PPE and the other with ELR. One of the patients developed

Grade IV PPE (Table 2). We now would like to present two of the six clinical cases, based on their special clinical features.

Clinical case1

A 73-year old woman with breast cancer first diagnosed in 2003 with bone metastases, received 5 cycles of PLD, 50 miligramme per square metre of body surface area (mg/ m^2) every four weeks for five cycles , two years after she underwent bilateral mastectomy. She was diagnosed with prurigo nodularis in 2000. Prurigo nodularis is a chronic eczematous process of unknown aetiology, characterized by a papulonodular pruriginous eruption and subsequent scar formation [12]. Five days after the last infusion of PLD, patient presented with a generalised erythema with erosions and bullae formation, preferentially at the sites of mechanical pressure. Skin eruptions were not restricted to hands and feet areas, but they were spread over the whole body including the capillitium and the axilla region. Due to prurigo nodularis patient also developed later bullae in the regions of preexisted scars and traumatized skin areas (Fig. 3). Tenderness, oedema as well as painful erythema and desquamation on both palms and soles were also observed (Fig. 1 and 2)

Two weeks after the fifth cycle of PLD the patient was diagnosed with cardiomyopathy with left ventricular ejection fraction (LVEF) of 31 per-cent (%). Cardiologic assessment was made by clinical examination, serial echocardiogram (ECG) and the measurement of LVEF obtained by echocardiography. Due to lack of previous clinical data, the unknown initial LVEF and pre-existing atrial fibrilation (AF), no secure correlation to the PLD therapy could be determined.

Clinical case 2

A 40 year-old woman was diagnosed with breast cancer in 1989 and underwent bilateral mastectomy in the same year. During the following years the patient received multiple cycles of other chemotherapeutic agents, including anthracyclines. In 2006 lung metastases were diagnosed and patient was treated with capecitabine until April 2007. A few weeks later she received PLD 50mg/m^2 infused in three cycles. One week after the third cycle, patient developed painful redness with desquamation, vesicules, macules and papules confined to hands and soles.The skin of the hands begun to peel. A few days later the maculopapular rash was spread to the axilla, trunk and extremities and patient had difficulties in picking up objects with her fingers, due to swelling and pain. At this stage, patient was hospitalised and low fever was recorded.

The diagnosis of ELR was established based on the histological findings, the subsequent blood tests which showed excessive lymphopenia and decreased (white blood cells) WBC coinciding with the rash, the negative immunofluorecence and the clinical signs.

Histological features

In four of six patients to evaluate the clinical diagnosis skin biopsies were performed in two papular, one papulovesiclar and one erythematous lesions. In connection with PPE, biopsies revealed unspecific changes such as mild spongiosis, sup-epidermal oedema, perivascular lymphocytic infiltration, dilated blood vessels, keratinocyte necrosis and presentation of eosinophils in the dermis. In one case there was also evidence of neutrophilic infiltrates of the sweat glands, compatible with neutrophilic eccrine hidradenitis. In the case of ELR, biopsy showed an atrophic epidermis with apoptotic keratinocytes, perivascular lymphocytic infiltration and interface dermatitis in the absence of eosinophils.

Therapy of skin reactions

All six patients required short-term hospitalizations and treatment for these skin reactions. The treatment consisted of supportive measures and various modalities during the hospitalization such as rest, avoidance of vigorous exercise and skin re-hydrating therapies. The medications included topic and systemic steroids, vitamin B6, topical antiseptic agents, urea 10 % ointment and emollient creams. These interventions led to a relief of the symptoms in all cases.

Management and outcome

Dose reduction was necessary in three patients, while only one patient was unable to continue the treatment due to painful skin eruptions and transient functional impairment. In one of the cases PPE presented at the end of the therapy with PLD (clinical case 1). Delays in administration of the chemotherapy for periods more than 1 week occurred in none of the patients. In one case an adjustment of the treatment intervals was required, and the time between the intravenous infusions of PLD 40 mg/m^2 was increased from every two weeks to every four weeks. Two of the patients have died in the meantime. The patient described in case one, died of multiple organ failure due to septicaemia several months after developing PPE.

Discussion

PPE is the most common cumulative toxicity experienced by the patients treated with PLD and appears to be dose-interval related. In their study Lyass et al. evaluated different incidence of PPE among patients during various treatment schedules and doses. Shorter schedules of drug administration lead to more severe symptoms and greater toxicity, which is not related to the dosage of PLD given at each cycle. At the dose schedule of 35mg/ m^2

administered every 3 weeks 17.7% of the patients developed PPE, while only 2.22% developed PPE at the dose of 50mg/ m^2 every 4weeks and at the dose of 65mg/ m^2 every 5 weeks [13]. Wollina et al. resumed that of the 34 patients who received PLD in different dosages, grade 2 and 3 PPE was observed in only 5.88% and 2.94% of the patients respectively [11]. Two out of 3 patients who developed PPE were on a 2-week schedule.

PPE was first reported in 1974 by Zuelke, during mitotane therapy [14]. It has been described that once PPE developes, can be recalled after treatment with other chemotherapeutic agents also known to cause this adverse effect [15]. It affects most commonly palms and soles, with hands being affected to a greater degree [16].

It is intriguing that pre-existing skin disease may facilitate the involvement of skin areas, other than hand and feet, as we have seen in the patient with pre-diagnosed prurigo nodularis. Patient described in clinical case one, developed bullae and vesicles on the pre-existing scars, which implies that compressed and damaged skin areas are faster and more intensely affected than normal skin. Preferential recruitment of liposomes to inflammateory areas was demonstrated in a murine model where liposomes were highly concentrated in areas around psoriatic lesion,which might be explained by the leakage of superficial post capillary venules in inflammatory areas [17].

In addition areas exposed to friction and to higher pressure such as axilla, groin, inner side of the knees, sacral area, bra line, elbow and wrist can be involved. This was also seen in the patient depicted in case one. The contribution of local trauma or pressure to the skin was reported in the study by Lyass et al [13]. PPE was manifestated in skin areas subjected to frequent contact pressure or microtrauma among 45 patients receiving PLD in different schedules and dosages, due to breast cancer [13].

Reduction of the dose of PLD is a standard approach to eliminate the risk of PPE [18]. Patient's education can also be very helpful [18]. Supportive treatment measures must start as soon as possible when the first signs of PLD adverse skin side effects occur, in order to relieve the symptoms and to avoid or/and reduce the severity of PPE [18]. Usually mild symptoms recede in one to three week. Non-pharmacologic interventions consist of sitting on padded surfaces, wearing loose clothing, and keeping the skin well hydrated. In addition avoidance of jogging or vigorous exercise and sunlight and use of regional cooling may have a positive effect in relieving the symptoms [19-21]. Emollients creams are of great value[22] while though corticosteroids and pyridoxine are used in clinical practice, their effects still remain to be cleared [23].

The eruption of lymphocyte recovery concurs with the return of the lymphocytes to the peripheral circulation and skin. It occurs more commonly after bone marrow ablative antineoplastic chemotherapy in leukaemia patients with a decrease in WBC count at a febrile patient [24]. The diagnosis of ELR should be based on both clinical and histological findings, as both are not specific [25]. It is manifestated as a generalised macular or papular rash, which reveals a non specific dermatitis in the biopsy. The histological features of ELR consist of a scan moderate superficial perivascular mononuclear infiltrate consisting predominantly of T-cells, followed by mild epidermal changes including slight basal vacuolization, intercellular oedema, atypical keratinocytes and dysmaturation [26]. With this article we for the first time depict a case of ELR in connection with therapy with PLD. The differentiation between ELR from drug eruption is of great significance since patients are often given multiple essential drugs when the rash occurs, especially in regard of initiating appropriate therapeutic measures.

Stomatitis was only present in one of the herewith presented patients, after two intravenous infusions of 85mg/m^2 of PLD (clinical case 6). The severity of stomatitis correlates strongly

with the dose and maximum plasma concetration (Cmax) and it is most often seen at doses around 60-70 mg/m^2. In the report of Al Batran et al. 22 of 45 enrolled patients developed grade 1-4 mucositis [27]. In addition Hamilton et al. showed that the reduction in the dose of PLD by administering higher doses at prolonged intervals (i.e. 60-70 mg/ m^2 every 6 weeks) was associated with significantly less PPE but higher rates of mucositis, ranging between 53 to 100%, including grade 3-4 mucositis in 12,5-85 % of patients [28].

Intertrigo-like dermatitis describes the development of rather painful erythematous patches at areas of skin folding such as axilla, belt region, groin and waist and resembles the manifestations of intertrigo. A case of a 60-year old woman treated with PLD that developed erythema at her axilla and groin, compatible with intertrigo like dermatitis has also been reported. The biopsy revealed interface dermatitis with epidermal dysmaturation [29].

In literature other skin reactions also correlated with PLD treatment are described. Harrison et al. reported alopecia in 8.8% of 34 patients receiving treatment with liposomal doxorubucin due to Acquired Immune Deficiency Syndrome(AIDS) related Kaposi sarcoma while Uzielly et al. described no cases of alopecia in two separate phase I studies of 56 patients [30] .Other skin manifestations of minor clinical significance include diffuse follicular rash, melanotic spots in unusual areas such as finger and toes webs, palms and soles, trunk, nail pigmentation, radiation- recall responses, hyperkeratosis and dry skin [13, 31, 32].

Conclusion

Pegylated liposomal doxorubicin induces various skin reactions including palmar plantar erythrodysesthesia syndrome. The exact clinical presentations might depend on pre-existing skin diseases. When skin reactions appear they may alter or affect patient's quality of life. However, they often respond to dose reduction and do not usually limit the duration of the

therapy. Finally palmar plantar erythrodysesthesia syndrome is frequent among patients treated with liposomal doxorubucin and as a result all physicians should be familiar with its clinical and histological manifestations, so that they can easily distinguish it from allergic drug reactions.

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Table 1. Grading of skin lesions according to National Cancer Institute common toxicity criteria (NCI CTC) version 3

Terminology	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**

Rash Desquamation	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms. localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular papular or vesicular eruption; desquamation Covering> 50% BSA	Generalised exfoliative, ulcerative or bullous dermatitis	Death

Table 2. Patients' demographic and clinical characteristics, dose intensity and impact of skin reactions on chemotherapy continuation.

Patient No	Age in years	PLD dose mg/m2	Intervals weeks	Localization	PPE grade	Onset of toxicity after Cycles	Consequences	Diagnosis	Other observations
1	71	100mg	4	S, I, P,C	IV	5	-	PPE	PN
2	40	50	2	S, P, A, E	III	3	stop	ELR	
3	56	30	4	P, S	II	3	reduction	PPE	
4	72	40	2	P, S, T	II	2	prolongation	PPE	SG inv.
5	56	50	4	I, E, P, S	III	3, 5	reduction	PPE	
6	29	85	4	I, OM,	II	2	reduction	ILD	Stom.

P palms, S soles, I intertriginous areas, A axilla, E extremities, OM oral mucosa, Capillitium, T thighs

PPE Palmar plantar erythrodysesthesia

ELR Eruption lymphocyte recovery

Stom. Stomatitis

ILD Intertrigo-like Dermatitis

SG inv. Sweat glands involvement

PN Prurigo nodularis

PLD Pegylated liposomal doxurubicin

Fig.1 Grade IV PPE with bullous formation and erosions at the feet of Pat.1

Fig.2　Grade IV PPE with bullous formation, painful edema and desquamation at both hands of Pat.1

Fig.3. Grade IV PPE with bullous formation and erosions on pre-existing scars at the trunk of Pat. 1